An Integrated Approach for Focal Cortical Dysplasia Lesion Validation on Preoperative Assessments

Josue D. Rodriguez
Electrical & Computer Engineering
Florida International University
Miami, FL, USA
jrodr1309@fiu.edu

Mercedes Cabrerizo
Electrical & Computer Engineering
Florida International University
Miami, FL, USA
cabreriz@fiu.edu

Marcos A. Bosques
Electrical & Computer Engineering
Florida International University
Miami, FL, USA
mbosq005@fiu.edu

Ilker Yaylali
Neurology
Oregon Health and Science University
Portland, Oregon
yaylalii@ohsu.edu

Malek Adjouadi
Electrical & Computer Engineering
Florida International University
Miami, FL, USA
adjouadi@fiu.edu

***Abstract*—Pediatric epilepsy due to drug-resistant Focal Cortical Dysplasia (FCD) presents significant healthcare challenges. Precise preoperative identification of FCD lesions is imperative for surgical planning and patient outcomes. This paper presents a proof-of-concept for an integrated methodology that combines Electroencephalogram (EEG)-based functional connectivity analysis with Magnetic Resonance Imaging (MRI)-derived cortical thickness measurements to identify FCD lesions in pediatric epileptic patients. We examined a single-case clinical scenario from Oregon Health Science and University, consistently identifying the Caudal Middle Frontal (cMFG) region across both EEG and MRI modalities, a finding that was confirmed in the postoperative MRI scan. This cross-validation underscores the potential of the precision of our approach in pinpointing the surgical target region. Despite being constrained by its preliminary nature, our research offers a valuable foundation for a personalized, rigorous method of detecting the location of the FCD lesions. It holds significant clinical implications for managing FCD-related epilepsy. It also portends broader applications in neurology and precision medicine. Nonetheless, further large-scale studies are needed to validate and fine-tune our methodology.**

***Clinical Relevance*—This study offers clinicians an advanced, integrated approach to preoperative assessment of FCD lesions, potentially improving the precision of surgical planning in pediatric epilepsy. The cross-validated accuracy in lesion localization could lead to enhanced seizure control, reduced postoperative complications, and improved patient outcomes.**

***Index Terms*—Focal Cortical Dysplasia (FCD), EEG-based Functional Connectivity, MRI-derived Cortical Thickness Measurements, Pediatric epilepsy, Precision Medicine**

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I. Introduction

Epilepsy, a neurological disorder impacting an estimated 50 million people worldwide, presents a significant public health burden [1]. Pediatric epilepsy uniquely exacerbates this burden due to a notable proportion of cases exhibiting resistance to existing antiepileptic drugs [2]. One common source of such drug-resistant epilepsy is Focal Cortical Dysplasia (FCD), characterized by recurrent, localized seizures that dramatically affect cognitive and behavioral development [3]. Therefore, developing efficacious diagnostic and treatment methodologies for FCD in children with epilepsy is paramount.

FCD is characterized by atypical cortical lamination and enlarged dysmorphic neurons, typically confined to a distinct brain region that becomes the epicenter of the seizures [4]. Traditionally, FCD lesions are localized using Magnetic Resonance Imaging (MRI). However, recent advancements have ushered in multimodal imaging approaches integrating MRI with PET, SPECT, and EEG [5]. Despite these strides, validating FCD lesions, particularly on an individual patient basis, remains a significant challenge contributing to suboptimal surgical outcomes.

The quest for improved FCD validation methods stems from various factors. Conventional neuroimaging techniques often inadequately capture the complex epileptic network standard in FCD cases, generally extending beyond the MRI-detectable lesions [6]. Despite its improved detection rate, multimodal imaging still struggles with precisely localizing the exact epileptogenic zone in complex FCD cases. This uncertainty often leads to incomplete resection during epilepsy surgery and persisting postoperative seizures.

To address these limitations, our research explores an integrated approach for validating FCD lesions in pediatric

patients with drug-resistant epilepsy. We propose an innovative approach that combines EEG-based functional connectivity analysis with MRI-derived cortical measurements. Integrating two distinct yet complementary data types is expected to enhance the accuracy and reliability of FCD lesion validation. The potential implications of our research are far-reaching. By creating a more accurate representation of neural behavior in epileptic generators, we aim to improve preoperative assessment processes and facilitate more precise surgical planning. This approach could improve seizure control, reduce postoperative complications, and enhance patient outcomes.

Beyond its immediate clinical application, our research holds broader implications for biomedical and health informatics. If proven successful, the proposed integrated approach could establish a standard for addressing similar challenges in diagnosis and treating various neurological disorders. Ultimately, our research aligns with the overarching goal of precision medicine, aiming to leverage technology to provide patient-specific diagnosis and treatment strategies that significantly enhance health outcomes.

II. Methods

A. Experiment Design & Patient Selection

Our experiment leverages a single-case clinical scenario using data from pediatric patients at Oregon Health and Science University. While this design limits generalizability, it primarily serves as a proof-of-concept, demonstrating the utility of our proposed integrated approach for identifying and validating FCD lesions. It thus lays a foundation for larger-scale research that our group is developing.

B. EEG Data Acquisition & Preprocessing

This study includes multichannel scalp EEG recordings from a single patient, collected using XLTEK Networks ver.3.0.5 equipment with a 10-20 electrode placement system and a sampling rate of 256 Hz. EEG signals were recorded from 19 electrodes: Fp1, F3, F7, T3, C3, T3, T5, P3, O1, Cz, Pz, Fp2, F4, F8, C4, T4, T6, P4, and O2. Parental written consent was obtained before participation, and the Institutional Review Board approved the study (Protocol number: IRB-052708-03).

EEG data preprocessing was performed to maximize brain-related activities and minimize unwanted sources. Preprocessing included DC-offset and slow drift removal, volume conduction reduction, and application of an infinite impulse response (IIR) notch filter at 60 Hz and a 4th-order Butterworth zero-phase digital filter within a range of [0.5 – 35] Hz. We employed Principal Component Analysis (PCA) and Independent Component Analysis (ICA) for artifact removal, identifying components based on their spatial and temporal characteristics [7]. We used the EEGLAB Toolbox within the MATLAB software environment to perform the preprocessing steps [8].

Interictal spikes were detected in 1-second EEG data segments, focusing on interictal discharge dynamics while eliminating background EEG propagation. Interictal spikes, crucial in analyzing epileptic seizures, help identify the location of seizure onset and its focal areas. An experienced epileptologist performed the visual identification of these spikes. This careful segmentation process forms the foundation of our functional connectivity analysis.

C. MRI Data Acquisition & Preprocessing

Raw DICOM file format of T1-weighted MRI was converted to the compact NIftI format using the dcm2niix toolbox [9]. FreeSurfer ver.6.0 (FS6) processed these images using the recon-all command to segment the T1-weighted MRIs, providing cortical thickness information for different brain regions [10].

D. Functional Connectivity Analysis

We performed functional connectivity analysis on the EEG data using Coherence algorithms presented mathematically in Equation 1. These algorithms measure the degree of synchronization between two signals as a function of frequency, with coherence values ranging from 0 (no correlation) to 1 (perfect correlation). The coherence values were transferred into an N×N (where N is the number of channels) functional connectivity matrix presented in Equation 2, wherein each cell represents the connectivity strength between a pair of electrodes.

$$C_{xy}(f) = \frac{|G_{xy}(f)|^2}{G_{xx}(f)G_{yy}(f)} \tag{1}$$

$$CM_{N\times N} = \begin{bmatrix} C_{11} & \cdots & C_{1N} \\ \vdots & \ddots & \vdots \\ C_{N1} & \cdots & C_{NN} \end{bmatrix} \tag{2}$$

E. Threshold Selection

Connectivity thresholds of 60%, 70%, 80%, and 90% were applied to the functional connectivity matrix based on previous studies demonstrating their effectiveness in distinguishing authentic neural connections from spurious correlations [11]. We considered resilience as the persistence of these connections at varying thresholds and defined genuine connections as those most likely to reflect actual neuronal communication rather than artifact noise.

F. Asymmetry Index

Using Equation 3, we calculated the asymmetry index of cortical thickness between the left and right hemispheres for different brain regions defined by the Desikan-Killiany atlas. Regions of interest where the asymmetry index exceeded the second standard deviation were identified based on established practices. In the context of FCD lesions, the asymmetry index can be a valuable indicator of cortical malformation, aiding in the validation of FCD lesions and providing insights into the epileptogenic zone.

$$AI = \frac{|LEFT - RIGHT|}{LEFT + RIGHT} \times 100 \tag{3}$$

III. Results

Our results underscore the potential utility and precision of an integrated, multimodal approach to validating Focal Cortical Dysplasia (FCD) lesions using EEG functional connectivity analysis and MRI-derived asymmetry indexing of cortical thickness. These findings, corroborated by preoperative and postoperative MRI scans, offer critical insights into FCD lesion validation.

Figure 1 presents topological maps of the functional connectivity between brain regions across different thresholds. The robust and resilient connections between electrodes C3, T3, T5, and P3 across various thresholds point to a potential locus of epileptic activity.

Figure 2 depicts the asymmetry index quantifying differences in cortical thickness values between the left and right hemispheres. This index maps the 34 regions delineated by the Desikan-Killiany atlas, with lower values indicating similarities in cortical thickness and higher values denoting differences. We marked abnormal cortical thickness differences where the asymmetry index exceeded the second standard deviation. Interestingly, the Isthmus Cingulate (ICC), Caudal Middle Frontal (cMFG), and Medial Orbito-Frontal (MOF) regions surpassed this threshold.

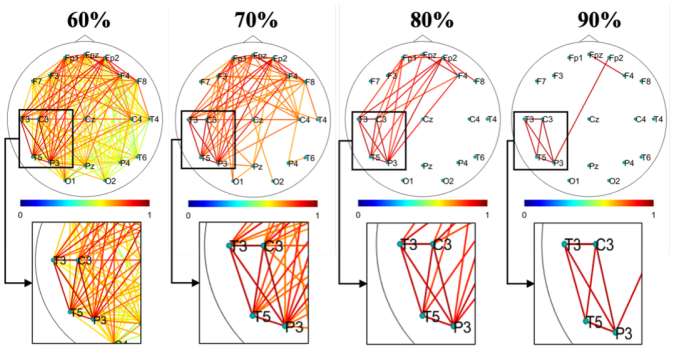

Fig. 1. Topological maps presenting functional connectivity analysis for different thresholds.

Figure 3 shows these regions of interest in the T1-weighted MRI, clearly delineating areas with abnormal cortical thickness. Upon close inspection of the data, the cMFG region consistently emerged in both the EEG and MRI data, suggesting its importance, and guiding our interpretation.

Figure 4 illustrates the difference between preoperative and postoperative MRI scans. The successful identification of the surgical target region in the preoperative scan, validated by the postoperative scan, attests to the accuracy of our methodology. This result underscores the potential of our approach to enhance preoperative assessment, facilitate precise surgical planning, and consequently, improve patient surgical outcomes.

IV. Discussion

Our study serves as a promising proof-of-concept, demonstrating the potential of an integrated approach in validating

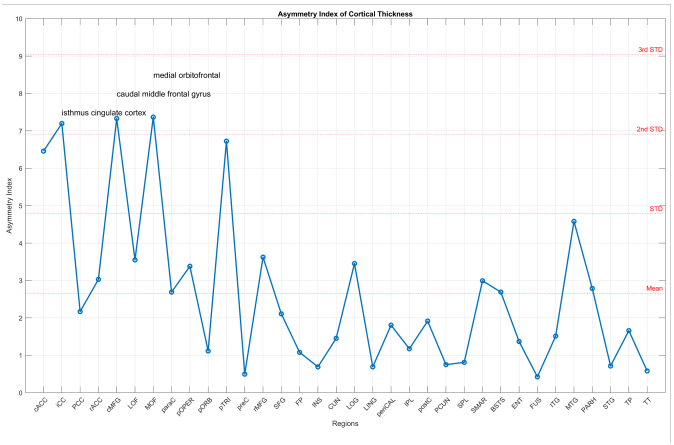

Fig. 2. Asymmetry index values for the 34-regions presented by the Desikan-Killiany Atlas.

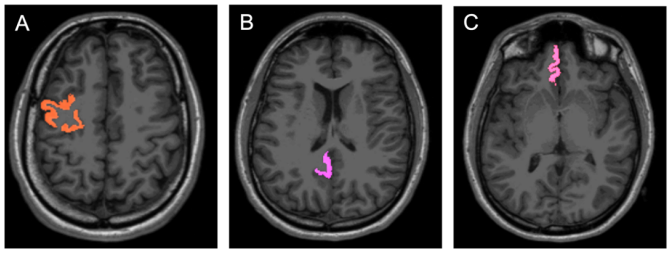

Fig. 3. Region of interest displayed in the T1-weighted MRI. (A) Caudal Middle Frontal (cMFG), (B) Isthmus Cingulate Cortex (ICC), and (C) Medial Orbitofrontal (MOF)

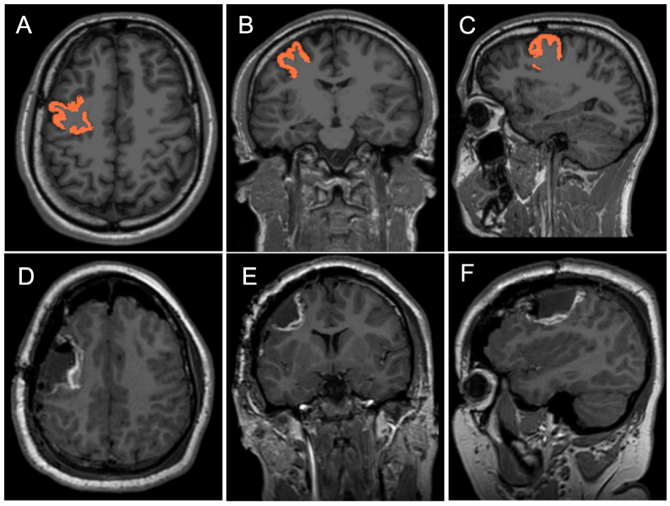

Fig. 4. Comparison between the preoperative and postoperative MRI scans. The highlighted region refers to the Caudal Middle Frontal (cMFG).

Focal Cortical Dysplasia (FCD) lesions. By incorporating EEG-based functional connectivity analysis with MRI-derived cortical thickness measurements, we propose a comprehensive method for preoperative assessment, facilitating more precise surgical planning and potentially enhancing patient outcomes.

The consistency of our EEG and MRI findings, particularly around the Caudal Middle Frontal (cMFG), underscores the value of such an integrated approach. Given the intricate networks in epilepsy and the often-inconspicuous nature of FCD lesions, the consistent identification of the cMFG region via both modalities strengthens our proposed methodology and the subsequent surgical strategy. The postoperative MRI scan confirmed these findings and further bolsters our confidence in this approach.

Moreover, our results illuminate the interconnected nature of the epileptic brain. The strong and resilient connectivity between electrodes C3, T3, T5, and P3, could offer insights into the organizational characteristics of the epileptic network and contribute to future research into mechanistic aspects of FCD-related epilepsy.

The clinical implications of these findings are substantial. By potentially reducing the chances of incomplete resection and subsequent seizure persistence, our approach could significantly improve the prognosis for pediatric patients with FCD-induced drug-resistant epilepsy. Consequently, this could enhance seizure control, decrease postoperative complications, and mitigate the cognitive and behavioral impacts of recurrent, localized seizures.

Beyond epilepsy and FCD, our proposed integrated approach may have broad applications within neurology. Similar multimodal strategies could be instrumental in identifying and characterizing a spectrum of neurological disorders, such as brain tumors, Alzheimer's disease, and other neurodegenerative conditions, where the precise localization of brain abnormalities is crucial. Our research thus significantly contributes to the burgeoning field of precision medicine, setting a precedent for future patient-specific diagnostic and treatment strategies.

While our study represents a crucial step forward, we acknowledge its limitations. Although the single-case design enables a detailed, individualized exploration, it requires validation through future studies involving more extensive, diverse patient samples. Refining our approach and addressing any unforeseen challenges will be crucial as we progress with our research. Despite these limitations, our study is pivotal in our journey toward a comprehensive and patient-centric approach to managing FCD-related epilepsy.

V. Conclusion

Our study has successfully demonstrated the feasibility and potential of an integrated multimodal approach in validating Focal Cortical Dysplasia (FCD) lesions in pediatric epilepsy patients. By amalgamating EEG-based functional connectivity analysis with MRI-derived cortical thickness measurements, we have illuminated a promising avenue for refining the precision of preoperative assessments and enhancing surgical planning. Despite the inherent limitations of a single-case design, our findings, underscored by the consistent identification of the Caudal Middle Frontal (cMFG) region across different modalities, establish a robust proof-of-concept. The correlation between our conclusions and postoperative results strengthens our approach's credibility and potential utility. Moreover, the possibility for broader applications of this method within the field of neurology represents an intriguing avenue for future exploration, contributing to the evolution of precision medicine and paving the way for patient-tailored treatment strategies. Moving forward, comprehensive research is required to validate, refine, and expand this methodology, ensuring its robustness and widespread applicability for diverse patient groups.

VI. Future Work

Our future research endeavors aim to further validate and optimize the presented methodology by applying it to a larger, more diverse cohort of patients. This expansion in scale will enable us to examine the robustness of our approach across varied clinical and demographic contexts. Furthermore, we plan to compare the efficacy of various functional connectivity analysis techniques and cortical measurements to fine-tune our methodology. Our overarching research goals remain centered around refining our approach, specifically focusing on devising an improved tool for personalized diagnosis and treatment strategies in epilepsy management. Ultimately, we aspire to contribute to enhancing patient outcomes and advancing the field of precision medicine in epilepsy and beyond.

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